Maturitas 72 (2012) 359–366

Contents lists available at SciVerse ScienceDirect

Maturitas

journal homepage: www.elsevier.com/locate/maturitas

A multinational study of sleep disorders during female mid-life

Juan E. Blümel[a], Antonio Cano[a], Edward Mezones-Holguín[a], Germán Barón[a], Ascanio Bencosme[a], Zully Benítez[a], Luz M. Bravo[a], Andrés Calle[a], Daniel Flores[a], María T. Espinoza[a], Gustavo Gómez[a], José A. Hernández-Bueno[a], Fiorella Laribezcoa[a], Mabel Martino[a], Selva Lima[a], Alvaro Monterrosa[a], Desiree Mostajo[a], Eliana Ojeda[a], William Onatra[a], Hugo Sánchez[a], Konstantinos Tserotas[a], María S. Vallejo[a], Silvina Witis[a], María C. Zúñiga[a], Peter Chedraui[a,b,*]

[a] *Collaborative Group for Research of the Climacteric in Latin America (REDLINC)*
[b] *Instituto Para la Salud de la Mujer, Facultad de Ciencias Médicas, Universidad Católica de Santiago de Guayaquil, Vélez 616 y García Avilés, PO Box 09-02000-70-A, Guayaquil, Ecuador*

ARTICLE INFO

Article history:
Received 18 May 2012
Received in revised form 23 May 2012
Accepted 24 May 2012

Keywords:
Menopause
Middle age
Sleep disturbances
Insomnia
Quality of sleep

ABSTRACT

Background: Although sleep disturbances are common during female mid-life, few studies have described in detail the prevalence of this problem and related risk factors.
Objective: To determine the prevalence of sleep disturbances in mid-aged women using validated tools. Assessment of determinants capable of influencing the prevalence of insomnia and poor sleep quality was also performed.
Methods: A total of 6079 women aged 40–59 of 11 Latin American countries were invited to fill out the Athens Insomnia Scale (AIS), the Pittsburgh Sleep Quality Index (PSQI), the Goldberg Anxiety and Depression Scale, the Menopause Rating Scale (MRS), the Brief Scale of Abnormal Drinking and a general socio-demographic questionnaire.
Results: Overall, 56.6% of surveyed women suffered of either insomnia, poor sleep quality, or both. Specifically, 43.6% and 46.2% presented insomnia and poor sleep quality in accordance to the AIS and the PSQI respectively. The prevalence of insomnia increased with female age (from 39.7% in those aged 40–44 to 45.2% in those aged 55–59, $p < 0.0001$) and menopausal stage (from 39.5% in premenopausal aged 40–44 to 46.3% in late postmenopausal ones, $p < 0.0001$). "Awakening during the night" (AIS: Item 2) was the most highly rated of all items and contributing in a higher degree (mean 16%) to the total score of the scale in all menopausal phases. Sleep quality also worsened with age and menopausal status, impairment particularly affecting sleep efficiency and latency and the increased use of hypnotics. Vasomotor symptoms (VMS), depressive mood and anxiety were associated to sleep disturbances. Women presenting sleep disturbances displayed a 2-fold increase in the severity of menopausal symptoms (higher total MRS scores) which was translated into a 6–8 times higher risk of impaired quality of life. Logistic regression analysis determined that female age, the presence of chronic disease, troublesome drinking, anxiety, depression, VMS, drug use (hypnotics and hormone therapy) were significant risk factors related to the presence of sleep disturbances. Higher educational level related to less insomnia and better sleep quality.
Conclusion: Insomnia and poor sleep quality were highly prevalent in this mid-aged female sample in which the influence of age and the menopause was only modest and rather linked to menopausal symptoms already occurring since the premenopause.

1. Introduction

Sleep disturbances are highly prevalent in the general population, and may particularly affect women and individuals with physical and/or mental health deterioration [1,2]. Therefore, it is not of surprise that the climacteric defines a period of high risk for sleep disturbances which may impair female quality of life (QoL). The Study of Women's Health Across the Nation (SWAN), a multiethnic female sample of 12,603, found that 38% of women aged 40–55 reported sleep difficulties significantly related to the menopause [3]. This percentage of affected women is higher than the 17.4% described in the general North-American population [4].

Sleep disturbances constitute a complex phenomenon, which may be *primary* (endogenously disrupted sleep-vigilance), or *secondary* (owing to psychological disorders, physical diseases, or the

* Corresponding author at: Instituto Para la Salud de la Mujer, Facultad de Ciencias Médicas, Universidad Católica de Santiago de Guayaquil, PO BOX 09-01-4671, Guayaquil, Ecuador. Tel.: +593 4 252 6825; fax: +593 4 220 6958.
E-mail addresses: peter.chedraui@cu.ucsg.edu.ec, institutochedraui@gmail.com (P. Chedraui).

0378-5122/$ – see front matter © 2012 Elsevier Ireland Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.maturitas.2012.05.011

use of drugs) [5]. Therefore during assessment it is important to use methods that aid at determining whether subjects complaining of insomnia suffer a sleep disorder or whether insomnia constitutes a symptom of some other mental disorder. Polysomnography is an objective method for the assessment of sleep disorders, nevertheless it does not allow self-evaluation of sleep quality or the impact that sleep disturbances may have over daytime functioning. Given the heterogeneity of sleep disturbances, various instruments have been developed that allow both quantitative and qualitative assessment of sleep quality and its impact on every-day life [6]. The SWAN also found that the prevalence of sleep disturbances was significantly related to ethnic origin, varying from 28% in Japanese women to 40% in Caucasians [3]. Bearing in mind the aforementioned aspects, our research group was interested in carrying out a multinational study to determine the prevalence of sleep disturbances in mid-aged Latin American women using validated tools. Assessment of determinants capable of influencing the prevalence of insomnia and poor sleep quality was also performed.

2. Methods

2.1. Participants and study design

This cross-sectional descriptive study was carried out among otherwise healthy Hispanic women aged 40–59 who accompanied patients attending 20 healthcare centres from cities with more than 500,000 inhabitants in 11 Latin American countries. Healthy status was defined according to criteria of the National Center for Health Statistics [7], as that enabling the performance of daily routine activities. Women with an ethnical origin distinct to Hispanic (i.e. Afro-American or Amerindian) or with a mental or physical handicap impairing the capacity of understanding the survey and/or providing answers were excluded. Those fulfilling inclusion criteria were requested to fill out the questionnaires after being informed about the research (and its purposes) and providing written consent in accordance with the Declaration of Helsinki [8]. The research protocol was reviewed and approved by the Bioethics Committee of the PROSAM Foundation, Santiago de Chile, Chile. EPI-INFO statistical software (EPI-INFO 6.04, 2001, Centers for Disease Control and Prevention, Atlanta, GA, USA) was used to calculate a minimal sample size of 184 women per centre considering that each covers an estimated population of 50,000 women [9] and assuming that 38% would present sleep disturbances [3] with an estimated 7% desired precision and a 95% confidence level. A minimum of 250 participants was requested to each centre.

2.2. Used instruments

2.2.1. General questionnaire

An itemized questionnaire was constructed to assess and record all general data. This tool was validated in 50 women before being implemented at the centres affiliated to the Collaborative Group for Research of the Climacteric in Latin America (REDLINC) participating in this study (REDLINC V). Each participating group was assigned a REDLINC centre number (city and country) (Appendix 1).

The general questionnaire included the following female data: age (years), marital status, educational level (years), parity, menopausal status, years since menopause onset, surgical menopause (yes/no) and current partner status (yes/no). Lifestyle and other personal factors included in this section were smoking habit, alcohol and coffee consumption, and physical activity. Medical care and drug use included: Past history of chronic diseases, psychiatric attention, and the use of oral contraceptives, psychotropic drugs and hormone therapy (HT) or alternative therapies for the menopause.

Insufficient educational level was defined as 12 or less years of study [10]. Menopausal status was defined using criteria of the Stages of Reproductive Aging Workshop (STRAW) [11]: premenopausal (women having regular menses); perimenopausal (irregularities > 7 days from their normal cycle); postmenopausal (no more menses in the past year). Women in the latter group were further categorized as early postmenopausal (1–4 years) and late postmenopausal (≥5 years). Premenopausal women were further categorized as younger or older than 45 years of age. Obesity was defined as a body mass index (BMI) ≥30 kg/m^2 and hypertension as blood pressure ≥140/90 mmHG or the use of antihypertensive drugs. Diabetes mellitus was identified among women if reporting so or due to the use of hypoglycemic drugs.

2.2.2. Validated tools

The Athens Insomnia Scale (AIS) [12] is a self-administered psychometric instrument designed for quantifying sleep difficulty based on the Classification of Mental and Behavioral Disorders ICD [13]. It consists of eight items: the first four pertain to sleep quantitative variables, including sleep induction, night awakenings, final awakening, and total sleep duration. The fifth item relates to sleep quality, and the last three refer to the impact of insomnia over day time performance. Items can be rated from 0 to 3, higher scores denoting more impaired sleep. The total score (sum of all rated items) may range from 0 to 24. A total AIS score of 6 or more was used to define insomnia. The AIS has been validated in Spanish by Nenclares and Jiménez-Genchi [14].

The Pittsburgh Sleep Quality Index (PSQI) [15] is another self-rated questionnaire which assesses sleep quality over the past 4 weeks. The PSQI does not evaluate the presence or absence of insomnia as the AIS, yet it distinguishes “poor” from “good” sleep through the measurement of seven components, including subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medications, and daytime dysfunction. The tool has 9 items, first four are scored according to the original manuscript [15]. Items 5–9 are rated by subjects from 0 to 3, where 3 indicate the most negative score. “Poor sleeper” is defined as a total PSQI score of 5 or more. The PSQI has been validated in Spanish by Macías Fernández and Royuela Rico [16].

The Menopause Rating Scale (MRS) [17] is a questionnaire that assesses the presence and intensity of 11 menopausal symptoms grouped into 3 subscales: the somatic subscale (4 items) assessing vasomotor symptoms (VSM, hot flushes and/or night sweats), heart discomfort, sleep problems, and muscle and joint discomfort; the psychological subscale (4 items), assessing depressive mood, irritability, anxiety, and physical and mental exhaustion; and the urogenital subscale (3 items), assessing sexual problems, bladder complaints, and vaginal dryness. Each of the 11 items can be rated as 0 (absent), 1 (mild), 2 (moderate), 3 (severe), and 4 (very severe). Scores obtained for the MRS (individual items, total and subscales) may be subjected to statistical calculations. Higher scores are indicative of more impaired QoL. A total MRS score of more than 16 points was defined as severe [18]. This questionnaire has been translated to 27 languages [19], and been validated in Spanish [20,21].

The Goldberg Anxiety and Depression Scale [22] aids in the diagnosis of anxiety and depression, discriminating and measuring the intensity of each component. It is composed of 2 subscales: the anxiety subscale (questions 1–9) and the depression subscale (questions 10–18) which are responded as affirmative or negative. It has been found that more than 4 affirmative answers in the anxiety and >3 in the depression subscale can respectively detect 73% and 82% of the cases of anxiety and/or depression in Latin

American populations [23]. The scale has been validated in Spanish by Montón et al. [24].

The Brief Scale of Abnormal Drinking [25] is widely used in Latin America to detect "troublesome drinkers", defined as alcohol drinkers whose behavior may affect the adequate performance of their work and endanger the physical and mental health of themselves and that of others. It contains 7 questions requiring an affirmative or negative answer, with 3 or more affirmative responses used to define a troublesome drinker.

2.3. Statistical analysis

Data analysis was performed using the EPI-INFO statistical program (Version 3.5.1 2008, Centers for Disease Control and Prevention, Atlanta, GA, USA; WHO, Basel, Switzerland). Results are presented as means (standard deviations) and percentages (95% confidence intervals, CI). The Kolmogorov–Smirnov test was used to assess the normality of data distribution and the Bartlett test to evaluate the homogeneity of the measured variance. According to this, group comparisons were performed with the Student's *t* test (two independent samples) or analysis of variance (several independent samples) for parametric data; and the Mann–Whitney *U* (two independent samples) or Kruskal–Wallis test (various independent samples) for nonparametric data. Percentages between groups were evaluated according to each case with the Chi-square test (straight or for the linear trend).

Logistic regression analysis was performed for the simultaneous assessment of several variables influencing sleep disturbances (insomnia and poor sleep quality as dependent variables). For this, AIS and PSQI scores were transformed into a categorical one, now considered as cases those exhibiting AIS scores $\geq$6 (insomnia) and/or PSQI $\geq$5 (poor sleep quality). Independent variables to be entered in the regression model were the following: depression/anxiety according to the Goldberg Scale (yes/no), current smoking > 4 cigarettes/day (yes/no), troublesome drinker (yes/no), obesity (yes/no), hypertension (yes/no), diabetes mellitus (yes/no), chronic obstructive pulmonary disease (COPD, yes/no), older age ($\geq$50 years, median), postmenopausal status (yes/no), surgical menopause (yes/no), VMS (yes/no), medication use (yes/no: oral contraceptives, HT for the menopause, hypnotic drugs), stable partner status (yes/no), low schooling ($\leq$12 years, yes/no). Entry of variables into the model was considered with a 20% significance level and the stepwise procedure performed. Interactions between significant variables found during regression model construction were also considered for the final model. Adequacy of the regression model was demonstrated with the Hosmer–Lemeshow goodness-of-fit test. For all calculations a p value of <0.05 was considered as statistically significant.

3. Results

During the study period a total of 6598 women were invited to participate. A 7.9% denied participation leaving 6079 complete surveys for statistical analysis. Main characteristics of participants are depicted in Table 1. Mean age and educational level of the entire sample was 49.8 ± 5.4 and 10.8 ± 4.9 years, respectively. Mean parity was 2.5, 68.9% had a stable partner, 57.6% were postmenopausal and 15.8% had surgical menopause. Overall, 55.5% of women displayed VMS, 13.2% used HT and 11.5% contraceptives. Concerning unhealthy habits, 11.3% currently smoked at least one cigarette per day and very few (0.1%) were troublesome drinkers. According to the Goldberg Scale, anxiety and depression affected 59.7% and 46.5%, respectively. A 23.9% of the women were using hypnotic drugs due to sleeping problems, 22.9% displayed hypertension, 18.5% obesity and 8.6% diabetes.

A 43.6% of all women suffered insomnia (AIS) and 46.2% poor sleep quality (PSQI). Globally, 56.6% of participants suffered sleeping problems (insomnia, poor sleep quality, or both) (Table 1). This table shows that women with sleeping problems were slightly older, less educated and more likely to be postmenopausal. In addition they used hypnotics and HT in a higher rate (38.0% vs. 5.6% and 15.6% vs. 10.2 respectively) and displayed a significantly higher rate of VMS (64.0% vs. 44.3%), depression (62.2% vs. 26.0%), anxiety (76.4% vs. 37.9%), obesity (21.6% vs. 14.6%), hypertension (26.0% vs. 18.8%), diabetes mellitus (10.4% vs. 6.3%), and chronic pulmonary obstructive disease (CPOD) (0.8% vs. 0.2%).

Table 2 shows that the prevalence of insomnia and poor sleep quality increased with age. Indeed, insomnia significantly increased from 39.7% in women aged 40–44 to 45.2% in those aged 55–59 (p = 0.009). Same trend was observed for poor sleep quality which increased from 40.3% to 49.3% (same age groups, p = 0.0001). Sleep disorders increased in a similar fashion in relation to menopausal status.

Total AIS scores significantly increased in relation to the menopausal stage, from 4.90 ± 4.57 in premenopausal women aged 40–44 to 5.81 ± 4.94 in late postmenopausal ones (p = 0.0001) (Table 3). Individually rated items of the AIS displayed a similar increasing trend. "Awakening during the night" (AIS: item 2) was the most highly rated of all items and contributed in a higher degree to the total AIS score for all depicted groups, but in particular for the young premenopausal (0.77 of 4.90 points, a 15.7%) and late postmenopausal group (0.94 of 5.81 points, a 16.2%). Score for item 1 ("difficulty with sleep induction") displayed a 32.8% increase in the late postmenopausal phase as compared to the early premenopausal one; this increment was the highest as compared to the other AIS items. Last three items of the AIS, which relate to daytime impact of insomnia, achieved the lowest scores and displayed the smallest percent increments throughout the menopausal stages.

Quality of sleep also displayed impairment in relation to the studied menopausal stage (Table 4). Total PSQI score increased from 4.28 ± 3.50 in premenopausal women aged 40–44 to 5.30 ± 3.89 in late postmenopausal ones (p = 0.0001). Day dysfunction (sleepiness) was the most highly rated item in premenopausal women aged 40–44 (0.99 of 4.28 points, a 23.1%) with a peak observed among peri- and early postmenopausal (1.10 and 1.08, respectively) and a lower value seen among late postmenopausal women, similar to that observed in young premenopausals (1.01). Scores for items of the PSQI exploring the need for sleep medication, sleep efficiency and sleep latency respectively displayed a 55.9%, 44.7% and 25.3% increase in the late postmenopausal phase as compared to the early premenopausal one.

The relationship between VMS intensity (assessed with item 1 of the MRS) and sleep disturbances are depicted in Table 5. AIS and PSQI scores increased in parallel with VMS intensity, with a near 2-fold increase observed in women presenting very severe VMS. Same trend was observed for the prevalence of sleep disturbances (insomnia and poor sleep quality).

AIS and PSQI scores were higher with increasing depression and anxiety scores, achieving values 3 times higher in women with very severe psychological symptoms (Table 6). Odds ratios (OR) for insomnia and poor sleep quality also displayed an increasing trend nearly 8- to 10-fold in relation to higher depressive and/or anxiety score. Interestingly, women with highest intensity of depression (score > 6) and anxiety (score > 9) paradoxically exhibited a lower rate of sleep disturbances than those with lower scores, and specifically with the prior group (depression 5–6 and anxiety 7–9) (p = 0.0001, Mann–Whitney). Although age, use of HT, anxiolytics, antidepressants, or hypnotics did not differ between these analyzed groups, percentage of VMS were significantly lower in those displaying depression scores higher than 6 (59.7% vs. 64.9%, p < 0.001, Chi-square). Same trend was observed for anxiety (55.6

Table 1
Characteristics of all studied women and according to the presence of sleeping problems.

	All women $n = 6079$ (100.0%)	Women with insomnia and/or poor quality of sleep		
		No $n = 2639$ (43.4%)	Yes $n = 3440$ (56.6%)	p Value*
Age (years)	49.8 ± 5.4	49.4 ± 5.4	50.1 ± 5.3	0.0001[1]
Educational level (years)	10.8 ± 4.9	11.0 ± 5.0	10.5 ± 4.8	0.0002[2]
Stable partner	68.9 (67.7–70.0)	68.4 (66.6–70.2)	69.2 (67.6–70.7)	NS
Parity	2.5 ± 1.5	2.4 ± 1.5	2.6 ± 1.6	NS
Postmenopausal	57.6 (56.4–58.9)	52.7 (50.8–54.6)	61.4 (59.7–63.0)	0.0001[3]
Surgical menopause	15.8 (14.9–16.7)	13.6 (12.3–15.0)	17.4 (16.2–18.8)	0.0001[3]
VMS	55.5 (54.2–56.7)	44.3 (42.4–46.2)	64.0 (62.4–65.6)	0.0001[3]
HT use	13.2 (12.4–14.1)	10.2 (9.1–11.4)	15.6 (14.4–16.8)	0.0001[3]
Contraceptive use	11.5 (10.7–12.4)	13.8 (12.5–15.2)	9.8 (8.8–10.8)	0.0001[3]
Current smoker	11.3 (10.5–12.1)	10.5 (9.4–11.8)	11.9 (10.8–13.0)	NS
Troublesome drinker	0.1 (0.1–0.3)	0.1 (0.0–0.4)	0.2 (0.1–0.4)	NS
Use of hypnotics	23.9 (22.9–25.0)	5.6 (4.8–6.6)	38.0 (36.3–39.6)	0.0001[3]
Depression (Goldberg)	46.5 (45.2–47.8)	26.0 (24.4–27.8)	62.2 (60.5–63.8)	0.0001[3]
Anxiety (Goldberg)	59.7 (58.4–60.9)	37.9 (36.0–39.8)	76.4 (74.9–77.8)	0.0001[3]
Obesity (BMI ≥30)	18.5 (17.6–19.5)	14.6 (13.2–16.0)	21.6 (20.2–23.0)	0.0001[3]
Hypertension	22.9 (21.8–24.0)	18.8 (17.3–20.4)	26.0 (24.6–27.5)	0.0001[3]
Diabetes	8.6 (7.9–9.4)	6.3 (5.4–7.3)	10.4 (9.4–11.5)	0.0001[3]
CPOD	0.6 (04–0.8)	0.2 (0.1–0.5)	0.8 (06–1.2)	0.002[3]

Data are presented as mean ± standard deviations or percentages (95% CI: confidence intervals); VMS, vasomotor symptoms; HT, hormone therapy; CPOD, chronic pulmonary obstructive disease, BMI, body mass index; NS, non-significant; SD, standard deviation; CI, confidence interval.
* p Value as determined with Student's t test[1], Mann–Whitney U test[2] or the Chi-square test[3].

Table 2
Prevalence of insomnia and poor sleep quality among studied women in accordance to age and menopausal status.

	All women $n = 6079$	Insomnia[1]% (95% CI)	Poor sleep quality[2]% (95% CI)
Age (years)			
40–44	1175	39.7 (36.9–42.5)	40.3 (37.4–43.1)
45–49	1692	43.1 (40.7–45.5)	45.3 (42.9–47.7)
50–54	1761	45.4 (43.0–47.7)	48.5 (46.1–50.9)
55–59	1451	45.2 (42.6–47.8)	49.3 (46.7–51.9)
p Value		0.009[3]	0.0001[3]
Menopausal stage			
Premenopause (40–44 years)	711	39.5 (35.9–43.2)	38.8 (35.2–42.5)
Premenopause (≥45 years)	949	36.5 (33.4–39.6)	41.0 (37.9–44.2)
Perimenopause	916	41.7 (38.5–45.0)	43.7 (40.4–47.0)
Early postmenopause	1758	47.4 (45.0–49.7)	48.5 (46.1–50.8)
Late postmenopause	1745	46.3 (43.9–48.7)	51.1 (48.7–53.5)
p value		0.0001[4]	0.0001[4]

[1]Athens Insomnia Scale: score ≥6; [2] Pittsburgh Sleep Quality Index: score ≥5; p value determined with Chi-square test for the linear trend[3] or straight Chi-square test[4].

Table 3
Scores for the Athens Insomnia Scale (total and per item) according to the menopausal stages.

AIS Items	Premenopause 40–44 years $n = 711$	Premenopause ≥45 years $n = 949$	Perimenopause $n = 916$	Early (<5 years) postmenopause $n = 1758$	Late (≥5 years) postmenopause $n = 1745$	p Value*
Difficulty with sleep induction	0.58 ± 0.76	0.67 ± 0.82	0.68 ± 0.82	0.75 ± 0.82	0.77 ± 0.86	0.0001[1]
Awakening during the night	0.77 ± 0.78	0.82 ± 0.79	0.90 ± 0.82	0.95 ± 0.83	0.94 ± 0.86	0.0001[1]
Early morning awakening	0.58 ± 0.73	0.57 ± 0.73	0.67 ± 0.81	0.71 ± 0.77	0.69 ± 0.79	0.0001[1]
Total sleep time (sufficiency)	0.66 ± 0.82	0.65 ± 0.80	0.70 ± 0.81	0.75 ± 0.83	0.74 ± 0.83	0.0070[2]
Overall quality of sleep	0.62 ± 0.77	0.65 ± 0.80	0.73 ± 0.81	0.72 ± 0.78	0.74 ± 0.82	0.0006[2]
Well-being during the day	0.52 ± 0.70	0.51 ± 0.73	0.60 ± 0.75	0.63 ± 0.76	0.62 ± 0.76	0.0001[1]
Functioning during the day	0.48 ± 0.66	0.48 ± 0.74	0.55 ± 0.73	0.57 ± 0.74	0.57 ± 0.72	0.0001[1]
Sleepiness during the day	0.67 ± 0.72	0.70 ± 0.77	0.73 ± 0.73	0.76 ± 0.75	0.76 ± 0.78	0.0259[1]
Total score	4.90 ± 4.57	5.03 ± 4.71	5.54 ± 4.75	5.84 ± 4.91	5.81 ± 4.94	0.0001[2]

Data are presented as mean ± standard deviations
* p Value as determined with the Kruskal–Wallis test[1] or ANOVA[2]; AIS, Athens Insomnia Scale.

vs. 65.6%, $p < 0.0001$, Chi-square). When women displaying only anxiety and/or depression (Goldberg test) were analyzed separately it was found that the presence of VMS increased insomnia risk 3.99 times (95% CI: 3.45–4.63) among anxious women and 2.33 times (95% CI: 1.98–2.74) among those depressed.

Relationship between the presence of sleep disturbances and menopause related QoL is depicted in Table 7. MRS scores (total and subscales) and the rate of those displaying severe total MRS scores (impaired QoL) were higher in women displaying both insomnia and poor sleep quality. Indeed, total MRS scores were found to be significantly higher in those with insomnia as compared to those without (12.21 ± 6.23 vs. 5.69 ± 4.75, $p = 0.0001$). Rate of women with impaired QoL was higher in women with insomnia (24.0% vs. 3.0%, OR: 10.32; 95% CI, 8.25–10.92). A similar trend was observed for poor sleep quality.

Risk factors related to insomnia and poor sleep quality after logistic regression analysis are depicted in Table 8. Logistic regression determined that troublesome drinking (OR: 5.27; 95% CI,

Table 4
Scores for the Pittsburgh Sleep Quality Index (total and per item) according menopausal stage.

PSQI items	Premenopause 40–44 years *n*: 711	Premenopause ≥45 years *n*: 949	Perimenopause *n*: 916	Early (<5 years) postmenopause *n*: 1758	Late (≥5 years) postmenopause *n*: 1745	*p* Value*
Duration of sleep	0.39 ± 0.72	0.44 ± 0.75	0.48 ± 0.77	0.46 ± 0.77	0.45 ± 0.75	NS
Sleep disturbance	0.97 ± 0.49	0.98 ± 0.53	1.02 ± 0.56	1.06 ± 0.56	1.06 ± 0.60	0.0001[1]
Sleep latency	0.91 ± 0.85	0.99 ± 0.88	1.05 ± 0.89	1.11 ± 0.89	1.14 ± 0.87	0.0001[2]
Day dysfunction (sleepiness)	0.99 ± 0.99	0.97 ± 0.91	1.10 ± 0.95	1.08 ± 0.94	1.01 ± 0.96	0.0005[2]
Sleep efficiency	0.47 ± 0.87	0.57 ± 0.94	0.51 ± 0.89	0.64 ± 1.01	0.68 ± 1.02	0.0001[1]
Overall sleep quality	0.94 ± 0.71	1.02 ± 0.71	1.02 ± 0.76	1.08 ± 0.75	1.09 ± 0.77	0.0001[1]
Need medication to sleep	0.34 ± 0.76	0.35 ± 0.82	037 ± 0.81	0.49 ± 0.94	0.53 ± 0.77	0.0001[2]
Total score	4.28 ± 3.50	4.62 ± 3.58	4.91 ± 3.75	5.24 ± 3.79	5.30 ± 3.89	0.0001[1]

* *p* value as determined with the Mann–Whitney *U* test[2] or ANOVA[1]; PSQI, Pittsburgh Sleep Quality Index.

Table 5
Relationship between intensity of VMS and sleep disturbances.

VMS score (MRS item 1)	No. women	Athens Insomnia Scale			Pittsburgh Sleep Quality Index		
		Score Mean ± SD	Insomnia % (95% CI)	OR (95% CI)	Score Mean ± SD	Poor sleep quality % (95% CI)	OR (95% CI)
0	2708	4.42 ± 4.63	32.2 (30.4–34.0)	1.00	4.21 ± 3.56	37.2 (35.4–39.0)	1.00
1	2097	5.81 ± 4.49	48.1 (46.0–50.3)	1.96 (1.73–2.21)	5.14 ± 3.56	48.8 (46.6–50.9)	1.61 (1.43–1.81)
2	934	7.13 ± 5.07	57.6 (54.4–60.8)	2.87 (2.45–3.35)	6.07 ± 3.86	58.4 (55.1–61.5)	2.37 (2.02–2.77)
3	266	8.31 ± 4.90	67.7 (61.7–73.3)	4.41 (3.33–5.85)	7.14 ± 4.18	68.4 (62.5–74.0)	3.66 (2.76–4.85)
4	74	9.34 ± 5.78	70.2 (58.4–80.2)	4.99 (2.92–8.57)	8.37 ± 5.08	70.3 (58.5–80.3)	4.00 (2.35–6.86)
p Value*		0.0001[1]	0.0001[3]	0.0001[3]	0.0001[2]	0.0001[3]	0.0001[3]

VMS, vasomotor symptoms; MRS, Menopause Rating Scale; SD, standard deviation.
* *p* value as determined with the Mann–Whitney test[1], ANOVA[2] and the Chi-square test[3]; VMS score (MRS item 1): 0: none, 1: mild, 2: moderate, 3: severe, 4: very severe.

Table 6
Insomnia and sleep quality in relation to depressive and anxiety scores of the Goldberg.

	No. women	Athens Insomnia Scale			Pittsburgh Sleep Quality Index		
		Score Mean ± SD	Insomnia % (95% CI)	OR (95% CI)	Score Mean ± SD	Poor sleep quality % (95% CI)	OR (95% CI)
Depression[a]							
0	1332	2.33 ± 2.66	13.4 (11.7–15.4)	1.00	2.46 ± 2.33	16.6 (14.7–18.7)	1.00
1–2	1311	4.00 ± 3.49	30.0 (27.5–32.6)	2.76 (2.25–3.38)	4.05 ± 2.95	34.1 (31.5–36.7)	2.60 (2.15–3.15)
3–4	1264	6.68 ± 4.51	56.7 (53.9–59.5)	8.44 (6.92–10.31)	5.78 ± 3.29	58.5 (55.7–61.2)	7.08 (5.86–8.55)
5–6	1046	8.15 ± 4.80	68.1 (65.1–70.9)	13.73 (11.11–16.97)	6.75 ± 3.82	68.3 (65.3–71.1)	10.81 (8.84–13.22)
>6	1126	7.48 ± 5.75	57.6 (54.7–60.5)	8.76 (7.15–10.75)	6.58 ± 4.43	61.1 (58.2–64.0)	7.90 (6.50–9.59)
p Value*		0.0001[1]	0.0001[2]	0.0001[2]	0.0001[1]	0.0001[2]	0.0001[2]
Anxiety[b]							
0	957	2.00 ± 2.51	12.5 (10.5–14.8)	1.00	2.13 ± 2.13	12.0 (10.1–14.3)	1.00
1–3	1104	3.41 ± 3.01	22.2 (19.8–24.8)	1.99 (1.55–2.55)	3.53 ± 2.50	30.1 (27.4–32.9)	3.15 (2.47–4.01)
4–6	1435	5.39 ± 3.90	42.7 (40.1–45.3)	5.20 (4.15–6.52)	4.82 ± 3.13	45.6 (43.0–48.3)	6.15 (4.89–7.73)
7–9	1478	8.44 ± 4.66	73.4 (71.1–75.6)	19.26 (15.28–24.29)	7.13 ± 3.74	72.6 (70.2–74.8)	19.40 (15.35–24.53)
>9	1105	7.09 ± 6.04	53.1 (50.1–56.1)	7.90 (6.26–9.99)	6.31 ± 4.39	57.4 (54.4–60.3)	9.86 (7.78–12.50)
p Value*		0.0001[1]	0.0001[2]	0.0001[2]	0.0001[1]	0.0001[2]	0.0001[2]

[a] Depression (score > 3 points for the Goldberg).
[b] Anxiety (score > 4 points for the Goldberg).
* *p* Values as determined with the Mann–Whitney *U* test[1] or the Chi-square test[2].

Table 7
Presence of sleep disturbances in relation to menopause related quality of life.

		MRS subscales (mean ± SD)			Total MRS Score	% Women with impaired QoL[c] (95% CI)	OR (95% CI)[d]
		Somatic	Psychological	Urogenital			
Insomnia [a]	No	2.29 ± 1.95	2.27 ± 2.31	1.13 ± 1.77	5.69 ± 4.75	3.0 (2.4–3.6)	1.00
	Yes	4.77 ± 2.55	5.21 ± 3.06	2.25 ± 2.24	12.21 ± 6.23	24.0 (22.4–25.7)	10.32 (8.25–10.92)
	p Value*	0.0001[1]	0.0001[1]	0.0001[1]	0.0001[1]		0.0001[2]
Poor Sleep quality[b]	No	2.36 ± 1.99	2.41 ± 2.39	1.23 ± 1.81	6.01 ± 4.97	3.9 (3.3–4.7)	1.00
	Yes	4.55 ± 2.62	4.88 ± 3.16	2.06 ± 2.24	11.49 ± 6.47	21.8 (20.2–23.3)	6.82 (5.56–8.38)
	p Value*	0.0001[1]	0.0001[1]	0.0001[1]	0.0001[1]		0.0001[2]

[a] Athens Insomnia Scale: score ≥6.
[b] Pittsburgh Sleep Quality Index: score ≥5.
[c] MRS total scores >16.
[d] Odds ratio when comparing those with and without sleep problems.
* *p* values as determined with the Mann–Whitney test[1] or the Chi-square test[2].

Table 8
Risk factors related to insomnia (AIS) and poor sleep quality (PSQI): logistic regression analysis.

Insomnia	OR	95% CI	Poor sleep quality	OR	95% CI
Troublesome drinker	5.27	1.14–24.51	Use of hypnotics	3.92	3.49–4.40
Anxiety (Goldberg)	3.57	3.09–4.14	CPOD	3.66	1.51–8.87
Depression (Goldberg)	2.39	2.10–2.72	Anxiety (Goldberg)	2.54	2.21–2.92
VMS	2.10	1.86–2.38	Depression (Goldberg)	2.48	2.17–2.83
Use of hypnotics	1.62	1.52–1.73	VMS	1.63	1.44–1.85
HT use	1.41	1.18–1.68	Age ≥50 years	1.19	1.06–1.35
Diabetes	1.37	1.11–1.68	Education >12 years	0.83	0.73–0.94
Education >12 years	0.84	0.74–0.9			

Logistic regression variables: depression (Goldberg), anxiety (Goldberg), smoker (>4 cigarettes/day), troublesome drinker, obesity, hypertension, diabetes, CPOD, older age (≥50 years), postmenopausal status, surgical menopause, VMS, use of HT, contraceptives or hypnotics, stable partner, education (>12 years). VSM, vasomotor symptoms; HT, hormone therapy; CPOD, chronic pulmonary obstructive disease; OR, odd ratios; CI, confidence intervals.

1.14–24.51), anxiety, depression, VMS, hypnotic use, HT use and diabetes mellitus were significant risk factors related to the presence of insomnia. The use of hypnotics (OR: 3.92; 95% CI, 3.49–4.40), the presence of CPOD, anxiety, depression, VMS and older age (≥50 years) were significant risk factors related to poor sleep quality. Higher educational level (>12 years) was an independent risk factor related to less insomnia (OR: 0.84; 95% CI, 0.74–0.95) and better sleep quality (0.83; 95% CI, 0.73–0.94).

4. Discussion

More than half of the participants of the present research were affected with insomnia and/or poor sleep quality. This slightly differs from a US study that found that 38% of women suffer sleep difficulties [3]. Nevertheless, the latter US finding was based on only one question assessing the previous 2 weeks. Using the Insomnia Severity Index (ISI) a recent study found that 41.5% of Ecuadorian women aged 40–59 suffer insomnia [26], a percentage similar to the 43.6% found in the present series. A Japanese study has reported that 50.8% of peri- and postmenopausal women suffer insomnia [27]. In this study sleep quality was self-rated by the participants in terms of sleep duration, sleep onset, sleep satisfaction and number of awakenings per night [27]. Finally, using the Women's Health Initiative Insomnia Rating Scale a Turkish study found that 54% of women aged 45–59 present sleep disturbances [28]. The aforementioned data from different regions of the world seem to conjunctly highlight the fact that about half of mid-aged women suffer sleep disturbances.

Our study also found that insomnia and poor sleep quality increased with age. However, the magnitude of this aggrandizement was only moderate since the increment observed between women aged 40–44 and 55–59 did not exceed 10%. Several European studies have also found that with age the prevalence of severe insomnia did not significantly increase or increased only very slightly [29–31].

The belief that sleep worsens around the menopause is widely shared by women and their clinicians. However, this topic is controversial. A well-regarded epidemiological study found that the menopause does not worsen sleep quality [32]. Nonetheless, using polysomnography and specific questionnaires, Kalleinen et al. [33] found that postmenopausal women had poorer sleep quality than younger women in their 20s. The investigators suggested that the changes could be related to the physiology of aging and not to the rapid changes seen across the menopause, since similar sleep characteristics were already present among premenopausal women. As with age, our study also found that the prevalence of insomnia and poor sleep quality increases in accordance to menopausal status. Our PSQI data seems to confirm that sleep efficiency (total hours of sleep/total hours in bed) and latency, and the increased use of hypnotic drugs were involved factors.

Analysis of scores obtained with the AIS highlights the fact that "awakening during the night" (item 2) most importantly influenced total AIS score and that score of item 1 assessing "difficulty with sleep induction" displayed the highest increase in the late postmenopause. Consistent with our data, a Korean study found that the most common symptoms of insomnia were difficulty in maintaining sleep (9.7%), difficulty at initiating sleep (7.9%) and early morning awakenings (7.5%) [34]. Similarly to this Korean study, our study found that diurnal impact of sleep disturbances in postmenopausal women is low. Xu et al. [35] have shown that menopausal Chinese women had lower sleep efficiency than non-menopausal ones (81.8% vs. 86.0%, respectively). A similar difference (80.2% vs. 84.3%) has been reported by Kalleinen et al. [33]. In our series, the AIS and the PSQ both failed at detecting daytime impact of sleep disturbances. Hence the menopause may slightly worsen sleep quality, but these disturbances do not substantially impact diurnal activities.

An interesting finding of our study was that VMS symptoms (a classical menopausal feature) significantly related to insomnia and poor sleep quality, despite observing a moderate effect of the menopause over the prevalence of sleep disturbances. The prevalence of sleep disturbances increased in parallel with the intensity of VMS. Insomnia prevalence (higher odds ratio) was significantly higher in women with severe VMS. The relationship between VMS and sleep disturbances has been reported by other investigators [3,26,36], as well as the direct association between VMS severity and insomnia prevalence [37]. Discrepancies found between epidemiological studies (describing a moderate or null impact of the menopause over sleep) and the contrary common belief of clinicians, seem to rely on the type of assessed population, the latter including the more symptomatic ones than the former. This hypothesis is further supported by the changing prevalence of insomnia reported in different countries. For instance, 37.2% in France and Italy, 27.1% in the US, as compared to only 6.6% in Japan [38], a country where VMS prevalence is lower than that observed in Western countries [39].

The present study also found that, similar to VMS, psychological symptoms such as anxiety and depression significantly relate to sleep disturbances. In the general population, anxiety has been asociated to a 4-fold increase in the risk for insomnia [40]. Depression occurs more commonly during the menopausal transition in women with VMS than in those without [41]; however most women with VMS do not develop depression. It has been hypothesized that VMS are associated with depression because these symptoms lead to repeated awakenings, which impair daytime well-being; however, in one study sleep disturbance seen in depressed participants was not consistent with the etiology of depression secondary to VMS-associated awakenings [42]. Likewise, a recent study has pointed out to the fact that mood symptoms seem to affect sleep independently of VMS [43]. The hypothesis that during the menopausal transition estradiol decline and

oscillations could be a common trigger for psychological symptoms, VSM, or sleep problems deserves attention [44]. The association seems well defined in the case of the VMS, although the detailed physiopathological steps are still obscure.

Changes in estradiol levels promote an elevated sympathetic activation that, acting through central alpha(2)-adrenergic receptors, contributes to the initiation of hot flashes, possibly by narrowing the thermoneutral zone [45]. Anxiety and depression have also been linked to estradiol fluctuations. The latter may affect neurotransmitter systems in brain regions that regulate mood [46]. Four distinct neurotransmitter systems have been shown to be affected during the menopause: gamma amino-butyric acid, serotonin, noradrenaline and dopamine [47]. It is of interest to mention that dopamine and serotonin have been implicated in the regulation of sleep [48], and that estrogen-dependent changes in serotonergic neuronal transmission during the menopausal transition have been cited as a possible cause for changes in sleep, mood and memory [49]. Supporting this hypothesis one can mention that experimental models confirm that the depletion of serotonin in the brain causes insomnia [50].

Good sleep quality is required for both good health and QoL [28,51]. Consequently, it has been shown that the severity of insomnia positively correlates with impaired health-related QoL [27]. The present study found that sleep disturbances associated with a 7- to 10-fold increase in the risk of impaired QoL, as assessed with the MRS, a specific instrument used for measuring QoL in mid-aged women. This QoL deterioration entails increased costs to the healthcare system due to a higher use of medical services, workplace absenteeism, increased risk for accidents and lower productivity [52].

Logistic regression analysis of the present study yielded alcoholism as a strong risk factor related to the presence of insomnia. Cohn et al. [53] found that 52 out of 57 investigated alcoholics suffered from sleep disorders. The use of hypnotics also emerged as an independent factor related to insomnia, a finding that may seem paradoxical given the proven effect of these drugs [54]. However, this observation has already been reported in the literature for HT [41] and also for hypnotics drug [55]. As a possible explanation, therapy is used by the most symptomatic subjects and, despite the proven benefit, the irregular use or the necessary adjustments required to meet the particular needs of a given patient may lead to a higher symptomatic prevalence than that observed in the general population. HT has shown efficacy against insomnia as well [54]; however the present study could not confirm this particular estrogenic effect. Important to mention is the fact that compared to Asian women [3], Latin American mid-aged women display a higher prevalence of VMS [41], a factor related to insomnia as already mentioned. Our logistic regression analysis also confirmed depression and anxiety as independent factors related to sleep disturbances. Finally, our study confirmed that education exerts a protective role against insomnia, a finding that has also been reported in a Brazilian study [56].

Our study is limited by its cross-sectional design, and consequently may only detect factors related to sleep disorders, but not causality. This hinders the clarification of the role of the menopause in sleep disturbances. Longitudinal studies have shown that sleep disturbances increase in the transition from the pre- to the postmenopausal status in women who did not comply with the use of HT [57].

The difference between cross-sectional and longitudinal studies could be influenced by the early onset of menopausal symptoms, prior to the cessation of menses. One recent study of our group [58] showed that among premenopausal women aged 40–44, 29.7% reported VMS, 44.3% depressive mood and 39.7% anxiety. Therefore, women entering the menopause are already considerably symptomatic, and this condition may favor insomnia or poor sleep quality. Another limitation of our study resides in the use of interviews that assess the perception that women have over their sleep quality. This perception does not always correlate with objective laboratory sleep measurements [59]. Nevertheless, the costs of this technology would be unsuitable for a study of the size of ours and, additionally, would miss the subjective perception of the sleep disturbance, a key element in the assessment of QoL.

In conclusion, nearly half of mid-aged women of this large sample presented sleep disturbances in which the influence of age and the menopause was only modest. Sleep disturbances were related more frequently to VMS, depressive mood and anxiety, symptoms which seem to be interrelated and linked to estrogenic changes already present in the premenopause. The impact of sleep disturbances over QoL was substantial.

Contributors

Juan E. Blumel, Edward Mezones-Holguín, Silvina Witis and Selva Lima were involved in the conception and design of the study. Germán Barón, Ascanio Bencosme, Zully Benítez, Luz M. Bravo, Andrés Calle, Peter Chedraui, Daniel Flores, María T. Espinoza, Gustavo Gómez, José A. Hernández-Bueno, Fiorella Laribezcoa, Mabel Martino, Selva Lima, Alvaro Monterrosa, Desiree Mostajo, Eliana Ojeda, William Onatra, Hugo Sánchez, Konstantinos Tserotas, María S. Vallejo, Silvina Witis, María C. Zuñiga conducted the clinical surveys. Juan E. Blumel performed the statistical analysis. Juan E. Blumel, Antonio Cano and Peter Chedraui performed drafting of the manuscript. All authors were involved in critically revising the manuscript for its intellectual content and approving the final version of the manuscript. Antonio Cano is an external (Spain) consulting member of the REDLINC.

Competing interests

None declared.

Funding

None.

Appendix A. Appendix 1

Participating *countries*, investigators and (City).

Argentina: María C. Zúñiga (Mendoza), Mabel Martino (Rosario) and Silvina Witis (Mendoza); **Bolivia:** Maria T. Espinoza (Cochabamba) and Desire Mostajo (Santa Cruz); **Chile:** Juan E. Blümel (Santiago de Chile), Daniel Flores (Santiago de Chile) and Maria S. Vallejo (Santiago de Chile); **Colombia:** German Baron (Bogota), Gustavo Gomez (Cali), Alvaro Monterrosa (Cartagena) and William Onatra (Bogota); **Dominican Republic:** Ascanio Bencosme (Santiago de los Caballeros); **Ecuador:** Peter Chedraui (Guayaquil), Hugo Sánchez (Machala) and Andres Calle (Quito); **Mexico:** Jose A. Hernandez-Bueno (Mexico, DF) and Luz M. Bravo (Guadalajara); **Panama:** Konstantinos Tserotas (Panama); **Paraguay:** Zully Benítez (Asunción); **Peru:** Eliana Ojeda (Cuzco), Fiorella Laribezcoa (Piura) and Edward Mezones-Holguin (Piura); **Spain:** Antonio Cano (Valencia); **Uruguay:** Selva Lima (Montevideo).

References

[1] Morin CM, LeBlanc M, Bélanger L, Ivers H, Mérette C, Savard J. Prevalence of insomnia and its treatment in Canada. Canadian Journal of Psychiatry 2011;56:540–8.
[2] Roy AN, Smith M. Prevalence and cost of insomnia in a state Medicaid fee-for-service population based on diagnostic codes and prescription utilization. Sleep Medicine 2010;11:462–9.

[3] Kravitz HM, Ganz PA, Bromberger J, Powell LH, Sutton-Tyrrell K, Meyer PM. Sleep difficulty in women at midlife: a community survey of sleep and the menopausal transition. Menopause 2003;10:19–28.
[4] Pearson NJ, Johnson LL, Nahin RL. Insomnia, trouble sleeping, and complementary and alternative medicine: analysis of the 2002 national health interview survey data. Archives of Internal Medicine 2006;166:1775–82.
[5] American Psychiatric Association. Diagnostic and statistical manual of mental disorders, DSM-IV, 4th ed. Washington, DC, American Psychiatric Association; 2000.
[6] Zhang L, Zhao ZX. Objective and subjective measures for sleep disorders. Neuroscience Bulletin 2007;23:236–40.
[7] Brett KM, Chong Y. Hormone replacement therapy: knowledge and use in the states unites. Hyattsville, MD: National Center for Health Statistics; 2001.
[8] World Medical and Association. Declaration of Helsinki. Journal of the American Medical Association 1997;277:925–6.
[9] CEPAL-ECLAC. Statistical yearbook for Latin America and the Caribbean. United Nations Publication: Santiago, Chile; 2011.
[10] CEPAL. Panorama Social de América Latina. Ed: CEPAL: Santiago, Chile; 2003. p. 66.
[11] Soules MR, Sherman S, Parrott E, et al. Executive summary: Stages of Reproductive Aging Workshop (STRAW). Climacteric 2001;4:267–72.
[12] Soldatos CR, Dikeos DG, Paparrigopoulos TJ. Athens Insomnia Scale: validation of an instrument based on ICD-10 criteria. Journal of Psychosomatic Research 2000;48:555–60.
[13] www.who.int/classifications/icd/en/bluebook.pdf.
[14] Nenclares A, Jiménez-Genchi A. Estudio de validación de la traducción al español de la Escala Atenas de Insomnio. Salud Mental 2005;28:34–8.
[15] Buysse DJ, Reynolds III CF, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Research 1989;28:193–213.
[16] Macías Fernández JA, Royuela Rico A. La versión española del Índice de Calidad de Sueño de Pittsburgh. Informaciones Psiquiátricas 1996;146:465–72.
[17] Heinemann K, Ruebig A, Potthoff P, et al. The Menopause Rating Scale (MRS) scale: a methodological review. Health and Quality of Life Outcomes 2004;2:45.
[18] http://www.menopause-rating-scale.info/documents/Ref_Values_CountrGr.pdf [accessed 01.05.12].
[19] http://www.menopause-rating-scale.info/languages.htm [accessed 01.05.12].
[20] Aedo S, Porcile A, Irribarra C. Calidad de vida relacionada con el climaterio en una población Chilena de mujeres saludables. Revista Chilena de Obstetricia y Ginecologia 2006;71:402–9.
[21] Chedraui P, Aguirre W, Hidalgo L, Fayad L. Assessing menopausal symptoms among healthy middle aged women with the Menopause Rating Scale. Maturitas 2007;57:271–8.
[22] Goldberg D, Bridges K, Duncan-Jones P, Grayson D. Detecting anxiety and depression in general medical settings. British Medical Journal 1988;297:897–9.
[23] Infomed. Red de Salud de Cuba. www.sld.cu/galerias/pdf/sitios/rehabilitacion/goldberg-depresion.pdf [accessed 23.11.11].
[24] Montón C, Pérez Echeverria MJ, Campos R, García Campayo J, Lobo A. Anxiety scales and Goldberg's depression: an efficient interview guide for the detection of psychologic distress. Atencion Primaria 1993;12:345–9.
[25] Orpinas P, Valdés M, Pemjeam A, Florenzano R, Nogueira R, Hernández J. Validación de una escala breve para la detección de beber anormal (EBBA). In: Florenzano R, Horwitz N, Penna M, et al., editors. Temas de Salud Mental y Atención Primaria de Salud. Santiago, Chile: CPU; 1991. p. 185–93.
[26] Arakane M, Castillo C, Rosero MF, Peñafiel R, Pérez-López FR, Chedraui P. Factors relating to insomnia during the menopausal transition as evaluated by the Insomnia Severity Index. Maturitas 2011;69:157–61.
[27] Terauchi M, Obayashi S, Akiyoshi M, Kato K, Matsushima E, Kubota T. Insomnia in Japanese peri- and postmenopausal women. Climacteric 2010;13:479–86.
[28] Timur S, Sahin NH. Effects of sleep disturbance on the quality of life of Turkish menopausal women: a population-based study. Maturitas 2009;64:177–81.
[29] Chevalier H, Los F, Boichut D, et al. Evaluation of severe insomnia in the general population: results of a European multinational survey. Journal of Psychopharmacology 1999;13:S21–4.
[30] Leger D, Guilleminault C, Dreyfus JP, Delahaye C, Paillard M. Prevalence of insomnia in a survey of 12,778 adults in France. Journal of Sleep Research 2000;9:35–42.
[31] Hajak G, SINE Study Group. Study of Insomnia in Europe. Epidemiology of severe insomnia and its consequences in Germany. European Archives of Psychiatry and Clinical Neuroscience 2001;251:49–56.
[32] Young T, Rabago D, Zgierska A, Austin D, Laurel F. Objective and subjective sleep quality in premenopausal, perimenopausal and postmenopausal women in the Wisconsin Sleep Cohort Study. Sleep 2003;26:667–72.
[33] Kalleinen N, Polo-Kantola P, Himanen SL, et al. Sleep and the menopause – do postmenopausal women experience worse sleep than premenopausal women? Menopause International 2008;14:97–104.
[34] Shin C, Lee S, Lee T, et al. Prevalence of insomnia and its relationship to menopausal status in middle-aged Korean women. Psychiatry and Clinical Neurosciences 2005;59:395–402.
[35] Xu M, Bélanger L, Ivers H, Guay B, Zhang J, Morin CM. Comparison of subjective and objective sleep quality in menopausal and non-menopausal women with insomnia. Sleep Medicine 2011;12:65–9.
[36] Savard J, Davidson JR, Ivers H, et al. The association between nocturnal hot flashes and sleep in breast cancer survivors. Journal of Pain and Symptom Management 2004;27:513–22.
[37] Ohayon MM. Severe hot flashes are associated with chronic insomnia. Archives of Internal Medicine 2006;166:1262–8.
[38] Leger D, Poursain B. An international survey of insomnia: under-recognition and under-treatment of a polysymptomatic condition. Current Medical Research and Opinion 2005;21:1785–92.
[39] Melby MK, Lock M, Kaufert P. Culture and symptom reporting at menopause. Human Reproduction Update 2005;11:495–512.
[40] Jansson-Fröjmark M, Lindblom K. A bidirectional relationship between anxiety and depression, and insomnia? A prospective study in the general population. Journal of Psychosomatic Research 2008;64:443–9.
[41] Blümel JE, Chedraui P, Baron G, et al. for the Collaborative Group for Research of the Climacteric in Latin America (REDLINC). A large multinational study of vasomotor symptom prevalence, duration, and impact on quality of life in middle-aged women. Menopause 2011;18:778–85.
[42] Joffe H, Soares CN, Thurston RC, White DP, Cohen LS, Hall JE. Depression is associated with worse objectively and subjectively measured sleep, but not more frequent awakenings, in women with vasomotor symptoms. Menopause 2009;16:671–9.
[43] Zervas IM, Lambrinoudaki I, Spyropoulou AC, et al. Additive effect of depressed mood and vasomotor symptoms on postmenopausal insomnia. Menopause 2009;16:837–42.
[44] Bourey RE. Primary menopausal insomnia: definition, review, and practical approach. Endocrine Practice 2011;17:122–31.
[45] Freedman RR. Hot flashes: behavioral treatments, mechanisms, and relation to sleep. American Journal of Medicine 2005;118:124–30.
[46] Freeman EW, Sammel MD, Lin H, Nelson DB. Associations of hormones and menopausal status with depressed mood in women with no history of depression. Archives of General Psychiatry 2006;63:375–82.
[47] Durant C, Christmas D, Nutt D. The pharmacology of anxiety. Current Topics in Behavioral Neurosciences 2010;2:303–30.
[48] Monti JM, Jantos H. The roles of dopamine and serotonin, and of their receptors, in regulating sleep and waking. Progress in Brain Research 2008;172:625–46.
[49] Krajnak K, Rosewell KL, Duncan MJ, Wise PM. Aging, estradiol and time of day differentially affect serotonin transporter binding in the central nervous system of female rats. Brain Research 2003;990:87–94.
[50] Delorme F, Froment JL, Jouvet M. Suppression of sleep with p-chloromethamphetamine and p-chlorophenylalanine. Comptes Rendus Des Seances De La Societe De Biologie Et De Ses Filiales 1966;160:2347–51.
[51] Kyle SD, Espie CA, Morgan K. "Not just a minor thing, it is something major, which stops you from functioning daily": quality of life and daytime functioning in insomnia. Behavioral Sleep Medicine 2010;8:123–40.
[52] Daley M, Morin CM, LeBlanc M, Grégoire JP, Savard J, Baillargeon L. Insomnia and its relationship to health-care utilization, work absenteeism, productivity and accidents. Sleep Medicine 2009;10:427–38.
[53] Cohn TJ, Foster JH, Peters TJ. Sequential studies of sleep disturbance and quality of life in abstaining alcoholics. Addiction Biology 2003;8:455–62.
[54] Terauchi M, Obayashi S, Akiyoshi M, Kato K, Matsushima E, Kubota T. Effects of oral estrogen and hypnotics on Japanese peri- and postmenopausal women with sleep disturbance. The Journal of Obstetrics and Gynaecology Research 2011;37:741–9.
[55] Englert S, Linden M. Differences in self-reported sleep complaints in elderly persons living in the community who do or do not take sleep medication. Journal of Clinical Psychiatry 1998;59:137–44.
[56] Marchi NS, Reimão R, Tognola WA, Cordeiro JA. Analysis of the prevalence of insomnia in the adult population of São José do Rio Preto, Brazil. Arquivos de Neuropsiquiatria 2004;62:764–8.
[57] Owens JF, Matthews KA. Sleep disturbance in healthy middle-aged women. Maturitas 1998;30:41–50.
[58] Blümel JE, Chedraui P, Baron G, et al. Menopausal symptoms appear before the menopause and persist 5 years beyond: a detailed analysis of a multinational study. Climacteric; in press.
[59] Philipsen A, Feige B, Al-Shajlawi A, Schmahl C, Bohus M, Richter H, et al. Increased delta power and discrepancies in objective and subjective sleep measurements in borderline personality disorder. Journal of Psychiatric Research 2005;39:489–98.